Differentiation of human embryonic stem cells to HOXA+ hemogenic vasculature that resembles the aorta-gonad-mesonephros.

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Funding Grants: A suite of engineered human pluripotent stem cell lines to facilitate the generation of hematopoietic stem cells

Public Summary:
The ability to generate blood forming stem cells from human pluripotent cells would enable many applications in research and treatment of patients. We find that blood forming cells derived from human embryonic stem cells (hESCs) lack critical regulatory genes, HOXA genes, compared to blood stem cells from human umbilical cord blood, indicating incorrect development. Using reporter stem cell lines to track the development of blood cells from blood vessel wall, we show that simultaneous modulation two signaling pathways yields blood forming cells with gene expression that more closely resembles that of cord blood. Our findings provide an approach to mimic in cell culture a key early stage in human blood lineage specification for the generation of blood stem cell like cells in couture.

Scientific Abstract:
The ability to generate hematopoietic stem cells from human pluripotent cells would enable many biomedical applications. We find that hematopoietic CD34+ cells in spin embryoid bodies derived from human embryonic stem cells (hESCs) lack HOXA expression compared with repopulation-competent human cord blood CD34+ cells, indicating incorrect mesoderm patterning. Using reporter hESC lines to track the endothelial (SOX17) to hematopoietic (RUNX1C) transition that occurs in development, we show that simultaneous modulation of WNT and ACTIVIN signaling yields CD34+ hematopoietic cells with HOXA expression that more closely resembles that of cord blood. The cultures generate a network of aorta-like SOX17+ vessels from which RUNX1C+ blood cells emerge, similar to hematopoiesis in the aorta-gonad-mesonephros (AGM). Nascent CD34+ hematopoietic cells and corresponding cells sorted from human AGM show similar expression of cell surface receptors, signaling molecules and transcription factors. Our findings provide an approach to mimic in vitro a key early stage in human hematopoiesis for the generation of AGM-derived hematopoietic lineages from hESCs.